REMARKS/ARGUMENTS

The foregoing amendments in the specification and claims are of formal nature, and do not add new matter.

Applicants note and appreciate the withdrawal of the earlier objections and rejections under 35 U.S.C. §112, second paragraph and rejections under 35 U.S.C. §102(b) and §103(a).

Prior to the present amendment, Claims 63, 66, 68-70 and 74-84 were pending in this application. With this amendment, Claims 78 has been amended to clarify what Applicants have always regarded as their invention. Claims 63, 66, 68-70 and 74-84 are pending after entry of the instant amendment.

Applicants believe that the current amendments place all claims in *prima facie* condition for allowance or, at least, in a better form for consideration on appeal. Accordingly, the consideration and entry of the present amendment after final rejection is respectfully requested.

Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

In addition, Applicants request the PTO to take note of the Revocation and Power of Attorney and Change of Address filed on March 7, 2003, and kindly direct all future correspondence to the address indicated, *i.e.*, to:

CUSTOMER NO. 35489
Ginger R. Dreger
Heller Ehrman White & McAuliffe LLP
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

Priority Determination

As previously set forth in the Applicants' response filed on November 18, 2004, Applicants rely on the gene amplification assay (Example 114) for patentable utility which was first disclosed in International Application No. PCT/US00/03565, filed February 11, 2000, priority to which has been claimed in this application.

The disclosure of the instant application, which is similar to that of the earlier-filed application, provides the support required to establish utility for the nucleic acid of SEQ ID NO:6

and fragments thereof. Hence, Applicants respectfully submit that the effective filing date of the present application is February 11, 2000.

Claim Rejections Under 35 U.S.C. §§101 and 112, First Paragraph (Enablement)

Claims 63, 66, 68-70 and 74-77 remain rejected and new Claims 78-84 are rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility." Specifically, the Examiner contends that "while the declaration and supporting references are convincing that the TaqMan realtime PCT method is very sensitive and can identify amplified genes, it is well known that aneuploidy is a common feature of most human cancers, and the data presented in the specification were not corrected for aneuploidy. A slight amplification of a gene does not necessarily mean overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid." See page 5 of the instant Office Action.

In addition, Claims 63, 66, 68-70 and 74-74 remain rejected and new Claims 78-84 are rejected under 35 U.S.C. §112, first paragraph, allegedly because one skilled in the art would not know how to use the claimed invention "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility."

For the reasons outlined below, Applicants respectfully disagree and traverse the rejections.

Utility – Legal Standard

According to 35 U.S.C. § 101:

> Whoever invents or discovers any new and *useful* process, machine, manufacture, or composition of matter, or any new and *useful* improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title. (Emphasis added.)

In interpreting the utility requirement, in *Brenner v. Manson*[1], the Supreme Court held that the quid pro quo contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent applicant disclose a "substantial utility" for his or

[1] *Brenner v. Manson* 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

her invention, *i.e.*, a utility "where specific benefit exists in currently available form."[2] The Court concluded that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. A patent system must be related to the world of commerce rather than the realm of philosophy."[3]

Later, in *Nelson v. Bowler*[4], the CCPA acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility."[5]

In *Cross v. Iizuka*[6], the CAFC reaffirmed *Nelson* and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results, *i.e.*, there is a reasonable correlation there between."[7] The Court perceived "no insurmountable difficulty" in finding that, under appropriate circumstances, "*in vitro* testing, may establish a practical utility."[8]

The case law has also clearly established that applicants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face.[9] The PTO has the initial

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[2] *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

[3] *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

[4] *Nelson v. Bowler*, 626 F. 2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

[5] *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

[6] *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

[7] *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.

[8] *Id.*

[9] *In re Gazave*, 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967).

burden that applicants' claims of usefulness are not believable on their face.[10] In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope."[11, 12]

Compliance with 35 U.S.C. §101 is a question of fact.[13] The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration.[14] Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

The well established case law is clearly reflected in the Utility Examination Guidelines ("Utility Guidelines")[15], which acknowledge that an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

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[10] *Ibid*

[11] *In re* Langer, 503 F.2d 1380,1391, 183 U.S.P.Q. (BNA) 288, 297 (CCPA 1974).

[12] See, also *In re* Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re* Irons, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

[13] *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984).

[14] *In re* Oetiker, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

[15] 66 Fed. Reg. 1092 (2001).

In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a '"substantial" utility'."[16] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement[17] gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Proper Application of the Legal Standard

The specification provides sufficient disclosure to establish a specific, substantial and credible utility for the nucleic acids encoding the PRO274 polypeptide.

Table 9 of Example 114 discloses that PRO274 showed approximately 1.00-1.61 ΔCt units which corresponds to $2^{1.00}$ -$2^{1.61}$ fold amplification or 2.0 fold to 3.053-fold amplification in three types of human primary lung tumors.

The Examiner has acknowledged that "the specification provides data that the PRO274 gene is overexpressed in three out of eighteen lung cancers (17%) at a level of two to about three fold over expression in normal lung tissue." Furthermore, the examiner has noted that the Wu Declaration "provides further support that mRNA is overexpressed in about 10% of all lung cancers of various different types and *could* possibly be useful as a cancer marker." See page 4 of the instant Office Action.

The Examiner contends that "slight amplification does not necessarily mean overexpression in a cancer tissue." Further, the Examiner contends that Dr. Wu's Declaration did not provide any information on the extent of overexpression of PRO274 mRNA in the cancer

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[16] M.P.E.P. §2107.01

[17] M.P.E.P. §2107 II (B) (1)

samples or how significant the overexpression is. The Examiner alleges that absent information about the degree of overexpression, the significance of the microarray data cannot be assessed.

Applicants respectfully disagree and traverse the rejection. The PTO is applying an incorrect standard. As discussed above, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, the question is not whether there is high degree of overexpression in a particular cancer sample, rather the test is whether it is more likely than not that a person of ordinary skill in the pertinent art would consider the gene overexpression in a number of cancer samples to be useful as a marker for the diagnosis of cancer.

Indeed, Applicants have previously submitted a Declaration by Dr. Audrey Goddard which clearly states:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

Therefore, any gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay would be considered useful as a marker for the diagnosis of cancer by one skilled in the art. Applicants have shown in their specification that PRO274 gene is amplified at least 2-fold in lung tumors. Accordingly, Applicants have shown that it is more likely than not that PRO274 is associated with lung tumors. In addition, Applicants provided Dr. Wu's Declaration which states that "for each type of lung tumor mentioned above at least 10% or greater of the patients with that type of lung tumor have overexpressed levels of PRO274 mRNA in their tissue samples compared to normal lung tissue samples from patients without lung cancer." Dr. Wu further states, "It is my considered scientific opinion that identifying patients having a gene, such as PRO274 gene that is overexpressed in at least 10% of the lung cancer

patients, would provide significant information for diagnosis and treatment since it would enable more accurate tumor classification and hence better determination of a suitable therapy."

Applicants respectfully submit that the case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew.[18] "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument"[19] Furthermore, the Federal Court of Appeals held in *In re Alton*, "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner"[20]. Applicants also respectfully draw the Examiner's attention to the Utility Examination Guidelines[21] which states, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered."

In the Declaration, Dr. Wu describes the experimental procedures and discloses that two groups of experimental data were generated for each microarray experiment. He further discloses that there were at least three sets of microarray experiments and that the expression levels of mRNA were determined. He indicates that for each type of lung tumor examined, at least 10% or greater of the patients with that type of lung tumor had overexpressed levels of PRO274 mRNA. He further indicates that overexpression in 10% of the patients is biologically significant as a lung tumor marker. Accordingly, Dr. Wu's statement that "[i]t is my considered scientific opinion that identifying patients having a gene, such as PRO274 gene that is overexpressed in at least 10% of the lung cancer patients, would provide significant information

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[18] *In re Rinehart 531* F.2d 1084, 189 USPQ 143 (CCPA 1976) and *In re Piasecki* 745 F 2d. 1015, 226 USPQ 881 (Fed. Cir. 1985)

[19] *In re Alton* 37 USPQ2d 1578 (Fed. Cir 1966) at 1584 quoting *In re Oetiker* 977 F 2d at 1445, u2 USPQ2d at 1444.

[20] *In re Alton*, supra

[21] Part IIB, 66 Fed. Reg. 1098 (2001)

for diagnosis and treatment" would be considered reasonable and accurate by one skilled in the art. Therefore, barring evidence to the contrary regarding the above statement in the Wu Declaration, Applicants do not have to provide additional information on the degree or level of overexpression in the cancer samples.

Further, Applicants respectfully submit that the amplification of the nucleic acids in even one lung tumor provides specific and substantial utility for the nucleic acid as a diagnostic marker of the type of lung tumor in which it was amplified. Applicants submit that the tumors listed in Table 9 are not similar tumors from different patients, but various types/classes of lung and/or colon tumors at different stages. Accordingly, a positive result from one tumor, where the nucleic acid was amplified, but not from other tumors, indicates that the nucleic acid can be used as a marker for diagnosing the presence of that kind of tumor in which it was amplified. Amplification of the nucleic acid would be indicative of that specific class of lung tumor, whereas absence of amplification would be non-conclusive.

The Examiner alleges that "the data presented in the specification were not corrected for aneuploidy." Therefore, the Examiner concludes that "[a] slight amplification of a gene does not necessarily mean overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid."

In response, Applicants refer to the previously submitted Declaration by Dr. Avi Ashkenazi, Ph.D. In particular, Dr. Ashkenazi is in opinion that gene amplification of a gene, whether by aneuploidy or any other mechanism, is still useful as a diagnostic marker. As a result, the present gene amplification assay is a well-controlled experiment and give rise to data of biological significance. As Dr. Ashkenazi explains,

> An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes.

The Examiner also alleges that "the asserted utility is not yet in currently available form. i.e., it is not substantial." The Examiner further alleges, "The proposed uses of the claimed

invention are simply starting points for further research and investigation into potential practical uses of the claimed nucleic acids."

Applicants respectfully disagree and traverse the rejection.

As stated above, in explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement.

Applicants have clearly shown that based upon the gene amplification results and Dr. Wu's Declaration that there is a clear correlation between the amplification and overexpression of the PRO274 gene and lung tumors. Accordingly, Applicants respectfully submit that Applicants' assertion that the claimed nucleic acids encoding the PRO274 proteins have utility in the field of cancer diagnostics is substantial.

In conclusion, Applicant submits that the present rejection is based on the application of an incorrect, elevated legal standard, on misconstruction of the references and erroneous conclusions drawn therefrom. The issue of patentable utility should be assessed on the totality of evidence, using the preponderance evidentiary standard. It is submitted that on the totality of evidence Applicants clearly established that the claimed invention has a substantial, specific and credible utility. Further, based on this utility and the disclosure in the specification, one skilled in the art at the time the application was filed would know how to use the claimed polypeptides. Accordingly, Applicants request the Examiner to reconsider and withdraw the rejection of Claims 63, 66, 68-70 and 74-84 under 35 U.S.C. §§101 and 112.

Claim Rejection Under 35 U.S.C. §112, First Paragraph (Written Description)

Claims 78-84 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) at the time the application was filed, had possession of the claimed invention. In particular, the Examiner alleges that "[t]he specification discloses only a single sequence, SEQ ID NO:6, that meets the limitations of the claims" and that "applicants have no conception of which of the thousands of possible nucleic acids would

hybridize to the nucleic acid molecule of SEQ ID NO:6." Therefore, the Examiner concludes that "the nucleic acid sequence of SEQ ID NO:[6], but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph.

Applicants respectfully disagree and traverse the rejection.

The Legal Test for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph, is "whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language."[22, 23] The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis.[24] The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure.[25, 26]

In *Environmental Designs, Ltd. v. Union Oil Co.*[27], the Federal Circuit held, "Factors that may be considered in determining level of ordinary skill in the art include: (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." (Emphasis added).[28] Further, the

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[22] *In re Kaslow*, 707 F.2d 1366, 1374, 212 USPQ 1089, 1096 (Fed. Cir. 1983)

[23] *see also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991)

[24] *See, e.g., Vas-Cath*, 935 F.2d at 1563; 19 USPQ2d at 1116.

[25] *Union Oil v. Atlantic Richfield Co.*, 208 F.2d 989, 996 (Fed. Cir. 2000)

[26] *See also* MPEP §2163 II(A).

[27] 713 F.2d 693, 696, 218 USPQ 865, 868 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984)

[28] *See also* MPEP §2141.03.

"hypothetical 'person having ordinary skill in the art' to which the claimed subject matter pertains would, of necessity have the capability of understanding the scientific and engineering principles applicable to the pertinent art."[29, 30].

The Disclosure Provides Sufficient Written Description for the Claimed Invention

Without acquiescing to the Examiner's position in the current rejections, Applicants have amended Claim 78 to recite, "An isolated nucleic acid molecule consisting of an at least 20 nucleotides fragment of the nucleic acid sequence of SEQ ID NO:6, or a complement thereof, that specifically hybridizes under stringent conditions to ...." Therefore, as amended, Claims 78 does not seek coverage of any nucleic acids that could be obtained under the specified stringent conditions, but claims a fragment of SEQ ID NO:6, or complement thereof. Further, as stated above, the Examiner has acknowledged that the nucleic acid sequence of SEQ ID NO:6 meets the written description provision of 35 U.S.C. §112, first paragraph.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the present rejections under 35 U.S.C. §112, first paragraph.

Claim Rejections – 35 U.S.C. §102(b)

As discussed above, Applicants respectfully submit that the effective filing date of the present application is February 11, 2000.

Claims 78-84 are rejected under 35 U.S.C. §102(b) as being anticipated by Ho *et al.*, Science, Vol. 289, pp 265-270 (publication date July 14, 2000). Applicants respectfully traverse this rejection. The Examiner contends that the Applicants' arguments previously submitted on November 18, 2004 is not deemed to be persuasive, "because the gene amplification assay fails to provide a patentable utility for the nucleic acid."

Applicants respectfully disagree and traverse the rejection.

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[29] *Ex parte Hiyamizu*, 10 USPQ2d 1393, 1394 (Bd. Pat. App. & Inter. 1988) (emphasis added)

[30] See *also* MPEP §2141.03

Applicants have amended Claim 78 to recite, "An isolated nucleic acid molecule consisting of an at least 20 nucleotides fragment of the nucleic acid sequence of SEQ ID NO:6, or a complement thereof, that specifically hybridizes under stringent conditions to ...." Therefore, as amended, Claims 78 only claims a fragment of SEQ ID NO:6, or complement thereof. Accordingly, Claims 78-84 are entitled to the effective filing date of February 11, 2000, and hence, Ho *et al.* is not prior art under 102(b) since its publication date is after the effective priority date of this application. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2630 P1C64**).

Respectfully submitted,

Date: April 22, 2005

By: _____
Anna L. Barry (Reg. No. 51,436)

HELLER EHRMAN LLP
275 Middlefield Road
Menlo Park, California 94025-3506
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

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